

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-337

CHEMISTRY REVIEW(S)

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-337 **CHEM. REVIEW #** 1 **REVIEW DATE:** 1/31/01

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL: yes	11/30/2000	12/1/2000	1/25/2001

NAME & ADDRESS OF APPLICANT:

Merck and Co Inc
P.O.Box 4
Sumneytown Pike, BLA 20 , West Point, PA 19486

DRUG PRODUCT NAME:

Proprietary: INVANZ

Nonproprietary: ERTAPENEM

USAN: ERTAPENEM SODIUM

Code Names /# 's : MK-0826, MK-826, L-749345, ZD4433, M251595 and
L-749345-002C

Chemical Type/

Therapeutic Class: 1s/

ANDA Suitability Petition/DESI/Patent Status:
N/A [if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION: Antibiotic
For the treatment of adults with infections caused by susceptible
pathogens.

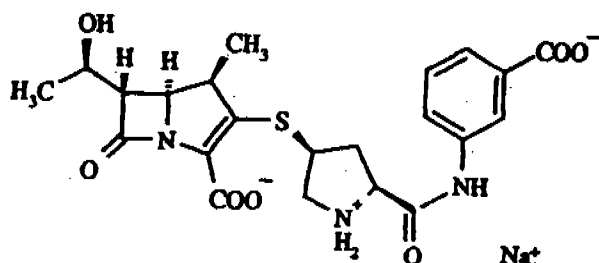
DOSAGE FORM: Injection

STRENGTHS: 1g

ROUTE OF ADMINISTRATION: Intravenous/Intramuscular.

DISPENSED: ☒ Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA.

Structural Formula**Molecular Formula:**

Monosodium salt - $C_{22}H_{24}NaN_3O_7S$

Free acid - $C_{22}H_{25}N_3O_7S$

Molecular Weight:

Monosodium salt - 497.50

Free acid - 475.50

1.1 Nomenclature

USAN Adopted Name: Ertapenem sodium

International Non-Proprietary Name: Ertapenem

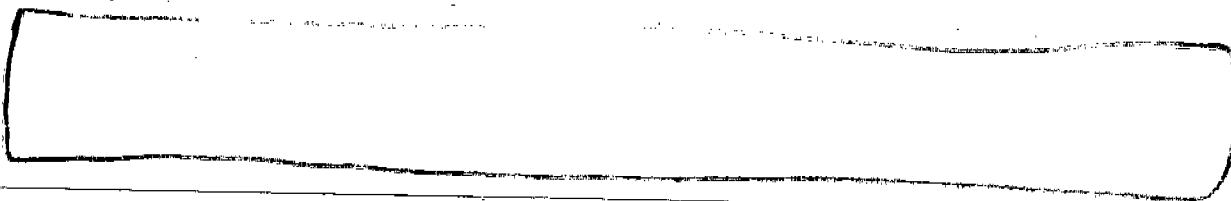
Chemical Name:

[4R-[3(3S*,5S*),4 α ,5 β ,6 β (R*)]]-3-[[[5-[[[(3-carboxyphenyl)amino]carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monosodium salt

Laboratory Codes: MK-0826, MK-826, L-749345, L-749345-002C

Chemical Abstracts Services (CAS) Registry Number: 153832-38-3

SUPPORTING DOCUMENTS:



RELATED DOCUMENTS (if applicable):

CONSULTS:

1. METHOD VALIDATION: Pending
It was sent to Philadelphia District Laboratory and San Juan District Laboratory, PR.

2. INSPECTION: Pending

EER has been requested on 1/30/2001

3. Trade Name: Pending

It has been requested

4. Sterility: Pending

It has been requested on 2/27/2001

REMARKS / COMMENTS:

INDICATIONS / COMMENTS:

INVANZ , a 1-beta -methyl carbapenem, is a new member of the beta-lactam class of antimicrobials. The firm states that pharmacokinetic and pharmacodynamic studies in animals suggest that the long-half life would allow for once daily dosing in man for infections caused by susceptible staphylococci, streptococci and gram negative pathogens. It is indicated for the treatment of complicated skin and skin structure infection : _____
_____, complicated intra-abdominal infection, acute pelvic infection, community acquired pneumonia and complicated urinary tract infection including pyelonephritis.

CONCLUSIONS & RECOMMENDATIONS:

UNAPPROVABLE

The firm should submit all the information enunciated under chemist's portion of the letter to the sponsor. The NDA is not approvable.

B.V. Shetty, Ph.D, Senior Review Chemist

cc:

Orig. NDA 21-337

HFD-520/Division File

HFD-520/B.V. Shetty/date

HFD-520/J. Alexander

HFD-520/K. Seethaler

HFD-520/J. Unowsky

HFD-520/G. Hills

HFD-520/F. Pelsor

HFD-830/C. Chen

HFD-520/D. Katague

**47 page(s) have been
removed because it
contains trade secret
and/or confidential
information that is not
disclosable.**

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-337 **CHEM.REVIEW #** 2 **REVIEW DATE:** 9/5/2001

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
------------------------	----------------------	------------------	----------------------

ORIGINAL:No Amendment	8/1/2001		8/16/2001
--------------------------	----------	--	-----------

NAME & ADDRESS OF APPLICANT:

Merck and Co Inc
P.O.Box 4
Sumneytown Pike, BLA 20 , West Point, PA 19486

DRUG PRODUCT NAME:

Proprietary: INVANZ

Nonproprietary: ERTAPENEM

USAN: ERTAPENEM SODIUM

Code Names / #'s : MK-0826, MK-826, L-749345, ZD4433, M251595 and
L-749345-002C

Chemical Type/

Therapeutic Class: Is/

ANDA Suitability Petition/DESI/Patent Status:
N/A [if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION: Antibiotic
For the treatment of adults with infections caused by susceptible
pathogens.

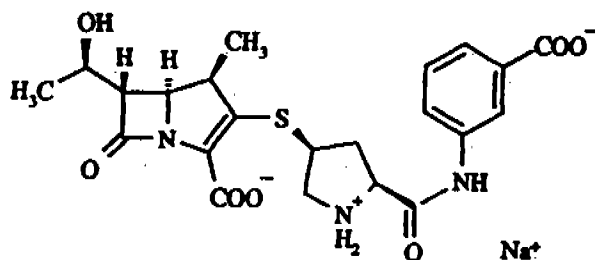
DOSAGE FORM: Injection

STRENGTHS: 1g

ROUTE OF ADMINISTRATION: Intravenous/Intramuscular.

DISPENSED: ☒ Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA.

Structural Formula**Molecular Formula:**Monosodium salt - $C_{22}H_{24}NaN_3O_7S$ Free acid - $C_{22}H_{25}N_3O_7S$ **Molecular Weight:**

Monosodium salt - 497.50

Free acid - 475.50

1.1 Nomenclature

USAN Adopted Name: Ertapenem sodium

International Non-Proprietary Name: Ertapenem

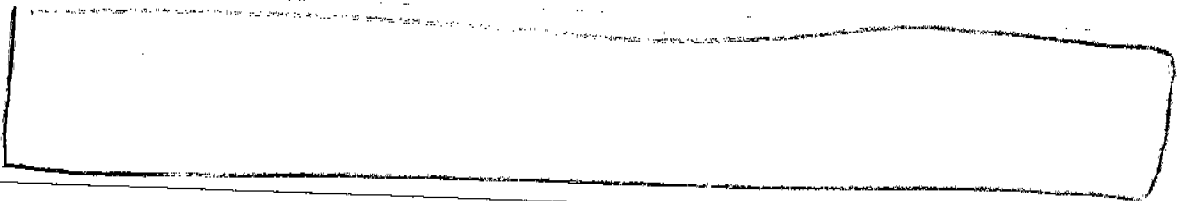
Chemical Name:

[4*R*-[3(3*S**,5*S**),4*α*,5*β*,6*β*(*R**)]]-3-[[5-[[[(3-carboxyphenyl)amino]carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monosodium salt

Laboratory Codes: MK-0826, MK-826, L-749345, L-749345-002C

Chemical Abstracts Services (CAS) Registry Number: 153832-38-3

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable):CONSULTS:NoneREMARKS / COMMENTS:

The current submission is the firm's response to the IR letter tele-faxed on July 9, 2001 as outlined in Chemist Review #1 dated 7/17/2001.

CONCLUSIONS & RECOMMENDATIONS:

APPROVABLE

The applicant has satisfactorily answered all the deficiencies stated in chemist review #1 dated 7/17/2001. NDA 21-337 is recommended for approval from CMC point of view. However, method validation, one of the facilities in EER reports and Sterility consult report are not yet completed.

B.V.Shetty, Ph.D., Senior Review Chemist
Date: 9/5/2001

HFD-520/Division File
HFD-520/B.V.Shetty/date
HFD-520/J.Alexander
HFD-520/K.Seethaler

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-337 CHEM. REVIEW # 3 REVIEW DATE: 11/2/2001

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
------------------------	----------------------	------------------	----------------------

ORIGINAL: No	8/1/2001		11/1/2001
Amendment			

NAME & ADDRESS OF APPLICANT:

Merck and Co Inc
P.O.Box 4
Sumneytown Pike, BLA 20 , West Point, PA 19486

DRUG PRODUCT NAME:

Proprietary: INVANZ

Nonproprietary: ERTAPENEM

USAN: ERTAPENEM SODIUM

Code Names / #'s : MK-0826, MK-826, L-749345, ZD4433, M251595 and
L-749345-002C

Chemical Type/

Therapeutic Class: 1B/

ANDA Suitability Petition/DESI/Patent Status:
N/A [if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION: Antibiotic
For the treatment of adults with infections caused by susceptible
pathogens.

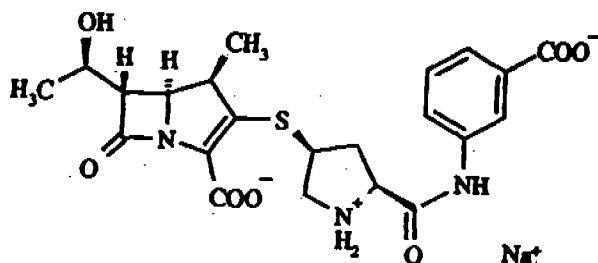
DOSAGE FORM: Injection

STRENGTHS: 1g

ROUTE OF ADMINISTRATION: Intravenous/Intramuscular.

DISPENSED: ☒ Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA.

Structural Formula**Molecular Formula:**Monosodium salt - $C_{22}H_{24}NaN_3O_7S$ Free acid - $C_{22}H_{23}N_3O_7S$ **Molecular Weight:**

Monosodium salt - 497.50

Free acid - 475.50

1.1 Nomenclature

USAN Adopted Name: Ertapenem sodium

International Non-Proprietary Name: Ertapenem

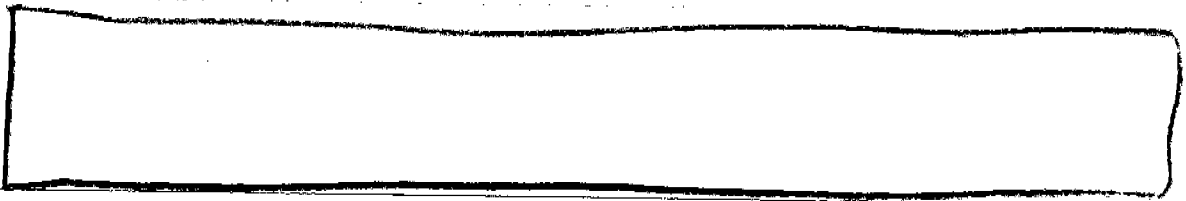
Chemical Name:

[4R-[3(3S*,5S*),4 α ,5 β ,6 β (R*)]]-3-[[5-[[[(3-carboxyphenyl)amino]carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monosodium salt

Laboratory Codes: MK-0826, MK-826, L-749345, L-749345-002C

Chemical Abstracts Services (CAS) Registry Number: 153832-38-3

SUPPORTING DOCUMENTS:



RELATED DOCUMENTS (if applicable):

CONSULTS: ADEQUATE

Micro was consulted. The Microbiology(HFD-805) Review dated October 17,2001 states that the firm (Merck) has adequately answered all the deficiencies and recommended approval.

REMARKS / COMMENTS: ADEQUATE

This Review #3, is the final concluding review of NDA 21-337. All reviews have been completed

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:**APPROVAL**

This is the final review of NDA 21-337
In summary:

1. Chemistry review #1 and #2 has concluded that all deficiencies have been adequately answered by the firm. This review # 3 summarizes all aspects of this NDA 21-337 with respect to CMC. The firm, as per agreement, has also submitted Certificate of Analyses for three manufacturing process validation batches of ertapenem drug substance and three validation batches of drug product three months prior to the user fee goal (PDUFA) date for NDA 21-337. They are adequate.
2. EER Report: All the facilities were inspected and were found to be ACCEPTABLE. See attached pages 5 to 8.
3. Micro Consult: As per final review #3 dated October 17, 2001, It was recommended for APPROVAL
4. Trade Name: The trade name, INVANZ, was found to be ACCEPTABLE.
5. Method validation: The method is being evaluated by the Philadelphia laboratory. It is still PENDING.

In summary, I recommend APPROVAL of this application for manufacturing and controls

B.V. Shetty, Ph.D., Senior Review Chemist
Date: 11/2/2001

HFD-520/Division File
HFD-520/B.V. Shetty/date: 11/2/2001
HFD-520/J. Alexander
HFD-520/K. Seethaler
HFD-520/J. Unowsky
HFD-520/CSO/Dillon-Parker
HFD-520/ F. Pelsor
HFD-520/D. Katague
HFD-520/S. Pagays/Acting T.L